Objections to the Specification

The specification was objected to for lacking a brief description of the Drawing. Applicants have amended the specification to include a brief description of the drawing and therefore respectfully request that this objection be withdrawn.

Rejections under § 112, second paragraph

Claims 6 and 7 have been rejected under 35 USC § 112, second paragraph as unclear as to what is considered a "suitable" signal peptide. The Examiner contends that it is unclear whether a signal peptide is suitable if any level of protein activity is found in the culture supernatant in step (b) or if one results in greater (or lesser) protein activity in the culture supernatant greater than a particular control or is a suitable signal peptide the one that provides the highest activity in step (b). Applicants respectfully traverse.

"Suitable" is defined by the American Heritage Dictionary as "appropriate to a given purpose or occasion." American Heritage Dictionary 1217 (2nd ed. 1991 Thus, one of skill in the art will determine, based on the relative activity of a signal peptide as defined in step d, whether such a peptide is suitable for the desired application, or desired purpose for which the peptide will be used. Depending on the desired application a signal protein may be suitable if any level of protein activity is found in the culture supernatant, or a suitable signal peptide may be the signal peptide that results in greater protein activity than another signal peptide, such as for example, the signal peptide with the highest activity. In order to meet the requirements of 35 U.S.C. § 112, second paragraph, the claims must define the patentable subject matter with a reasonable degree of particularity and precision. M.P.E.P. § 2173.02. The primary purpose of this requirement of definiteness of

claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. M.P.E.P. § 2173. The ordinary meaning of the term suitable as used in claim 6 clearly defines the boundaries of what constitutes infringement. Thus, Applicants respectfully request that these rejections be withdrawn.

The Examiner also rejected claim 6 arguing that step (b) is unclear as to the nexus of the expression rate and the activity of the protein in the culture supernatant. The Examiner argues that it is unclear whether the protein is active with the secretory signal attached or must the secretory signal be removed. According to the Examiner, it is also unclear whether the protein activity in the culture supernatant represents all of the protein that was secreted with or without signal peptide intact or only those proteins that were secreted and in which the signal peptide was removed. Applicants respectfully traverse.

The exact nexus of the expression rate to the activity of the protein is not necessary to define the patentable subject matter of claim 6 with a reasonable degree of particularity and precision. As stated in step (c) of claim 6, steps (a) and (b) are "repeated." Step (d) of claim 6 then requires that the suitable signal peptide is selected by comparing the expression rates found in step (b). Thus, as long as one uses a consistent method of determining expression rate from protein activity or compensates for any differences in the determination of expression rate from protein activity, the exact nexus of the expression rate to the activity of the protein is not necessary and the boundaries of what constitutes infringement are clearly defined. Thus, Applicants respectfully request that these rejections be withdrawn.

Claim 8 was rejected as unclear as to the meaning of "expression." Applicants thank the Examiner for pointing out this error. Claim 8 has been

amended the to correct this typographical error and thus Applicants respectfully request that this rejection be withdrawn.

Rejections under § 112, first paragraph

Claims 6-8 were rejected under 35 USC § 112, first paragraph because the specification does not reasonably provide enablement for a process for selecting a suitable signal peptide for secretory expression of any desired protein using the method steps of the claims. Applicants respectfully traverse.

The Examiner admits that the instant application is enabling for a process for selecting a suitable signal peptide for secretory expression of hirudin or a hirudin derivative using the method steps of the claims. Thus, the Examiner admits that a skilled artisan can practice the steps of the claims, and the Examiner's rejection is based on her contention that undue experimentation would be required to determine whether a signal peptide selected as suitable for hirudin expression would be suitable for expression of other desired proteins. Official Action, p. 6. In other words, the Examiner appears to be rejecting the claims on the basis that once a signal peptide was chosen as suitable by the methods of the instant invention, it would be undue to determine if that signal peptide was suitable for expression of other proteins. Applicants respectfully disagree.

In the instant invention, hirudin concentration is a direct measure of the efficiency of secretion and thus elimination of the signal peptide. More specifically, since hirudin cannot be efficiently released into the supernantant via the signal peptide of the CGTase, the use of hirudin provides a model system to test for a signal peptide which permits release of hirudin, *i.e.*, a signal peptide that can be recognized and turn on secretion. Since little or no release of hirudin occurs without

the addition of a suitable signal peptide, the release of hirudin would signal processing of the carboxy-terminal amino acid of the signal peptide. Whether the system recognizes the carboxy-terminal amino acid of the signal peptide should for the most part be independent of the peptide attached to the signal peptide. Thus, the present invention provides a good predictor of whether the signal peptide is suitable for other proteins.

The Applicants are not claiming that all signal peptides determined suitable by the methods of the invention will be suitable for secretory expression of all proteins. Nonetheless, claims are not necessarily invalid even if they encompass some inoperative embodiments. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.* 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Moreover, determining whether a signal peptide selected as suitable by the methods of the invention would be suitable for expression of other desired proteins only requires routine skill. Experiments such as those described in the present specification and in the *Wong* reference cited by the Examiner could be easily performed to determine whether other proteins are secreted. Routine or guided experimentation do not constitute undue experimentation. M.P.E.P. § 2164.01; 2164.01(a).

To summarize, the methods of the present invention provide a preliminary screen which determines whether a signal peptide is recognized and processed, and therefore provides a strong indication of whether of not a signal peptide may have general applicability. The applicability to a specific protein in *E. coli* can then be tested in routine experiments. Therefore, the specification provides full 35 U.S.C. § 112, 1st paragraph support for the claimed invention.

Rejections under § 103

Claims 6, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Achstetter et al. in view of Schmid et al. Applicants respectfully traverse.

The Examiner contends that Aschetter et al. discloses a method of selecting a signal peptide for secretory expression of hirudin or a hirudin derivative comprising (a) expressing in a culture medium hirudin connected to a signal peptide, (b) determining the expression rate by measuring protein activity, (c) repeating steps (a) and (b) with various signal peptides, and (d) selecting the suitable signal peptide by comparing the expression rates found in (b). The Examiner admits that Achstetter et al. only teaches expression in yeast and not in *E. coli*. However, the Examiner argues that Schmid et al. teaches expression of hirudin in *E. coli* is advantageous over using yeast, thus it would be obvious to one of ordinary skill in the art at the time of the invention to use the process of Achstetter et al. in *E. coli*. According to the Examiner, one of ordinary skill in the art would have been motivated to use *E. colil* in the method of selecting signal peptides because Schmid et al. discloses the advantages of *E. coli*. Applicants disagree.

The fundamental basis of the Examiner's argument is that because of the disclosure in Schmid et al. of the advantages of *E. coli*, one of skill in the art would have been motivated to perform the process of Achstetter et al in *E. coli*. Applicants disagree with this characterization of Scmidt et al. Applicants respectively point out that the Examiner is only selectively choosing passages from Schmid et al. and not considering the reference as a whole as required. While Schmid et al. at col, 2, line 15-16 does state that cultivation in yeast cells takes longer than *E. coli*, in the following sentence Schmid also states that the yield in *E. coli* is relatively low and the isolation processes are complicated. The aim of Achstetter et al, as pointed out in

the passage referred to by the Examiner, was to increase hirudin productivity. Achstetter et al p. 26, col. 1, line 27-30. In view of the Schmid et al. admission that *E. coli* results in low yield there is certainly no motivation from Schmid et al. to perform the process of Achstetter et al in *E. coli.*

The Examiner appears to overlook this disclosure in Schmid et al by pointing to Col. 3, lines 32-34 which he characterizes the reason for the preference of *E. coli* as *E. coli* strains which show massive protein secretion. Official Action p. 9. However, these special *E. coli* strains are mutants specifically chosen to provide optimum secretion with signal peptides are known to allow permeation of the membrane of *E. coli* cells. Schmid et al, col 3, line 32, to col. 4, line 11. Aschtetter et al, on the other hand, uses signal peptides from a group of certain deletion mutants of the alpha-factor of yeast. Thus, there would be no motivation to use the yeast signal peptides of Aschtetter et al. in the specific system of Schmid et al., which is optimized for *E.coli* signal peptides.

In summary, when the Schmid et al reference is considered in its in entirety it fails to provide the requisite motivation to use *E. coli* in the system of Aschtetter et al. In actuality, Schmid teaches away from the use of *E. coli* in the system of Aschtetter et al. Thus, Applicants respectfully request that these rejections be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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